The Commonwealth of Massachusetts
Department of Public Health
600 Washington Street
Boston 02111

Alfred L. Frechette,M.D.,MPH
Commissioner

MEMO

TO: Gregory Connolly, D.M.D., M.P.H.
Director, Division of Dental Health

John Cutler, M.D., Director
Division of Environmental
Health Assessment

FROM: Martha Steele, M.P.H.

RE: Water Fluoridation and Reproductive Outcomes

DATE: May 23, 1983

The Division of Environmental Health Assessment was asked to evaluate whether fluoridated water could have adverse effects of human reproductive outcomes. This memo summarizes the results of the evaluation.

1. Fluoride intake, distribution and metabolism (from Smith et al, 1982).

Intake - On the average, where water supplies contain about 1 mg fluoride/ liter water, consumption of 1 liter of water contributes roughly 1/2-2/3 of the total daily intake of fluorides.

Absorption - 88-95% of the intake is rapidly absorbed from the gastro-intestinal tract.

Distribution - Fluorides in the body exist both as ions and, more often, in a protein bound form. It is not known whether there is a difference in the toxicity between the two forms. In one study with human subjects, 60 minutes after ingestion, 40% of the dose was in the extracellular fluid, 20% was excreted and 20% was taken up in the tissues. Fluoride is stored in sites of calcification and not in soft tissue. It is rapidly deposited in the skeleton. Immobilization of fluoride by skeletal deposition is a detoxification mechanism. This is a faster detoxification mechanism than urinary excretion.

From the time bone mineral first appears during fetal life, the development of the collagen fibers may depend on very small amounts of fluoride. It is estimated that the skeletal fluoride half-life is about 8-10 years.

2. Fluoride metabolism in pregnant women and the fetus.

Fluoride undoubtedly crosses the placenta. No studies exist on the effect of fluoride on the human placenta, and it is not known whether the placenta regulates the amount of fluoride to the fetus.

Studies from Shen and Taves (1974) have shown that the fluoride ion concentrations in fetal cord blood are about 75% that of maternal blood.

Once in the fetus, fluoride is readily taken up by the calcifying fetal bones and teeth. In a recently published article, data on the distribution and excretion pattern of fluorides in pregnant and non-pregnant women were reviewed. It was concluded there was little difference between the two (per conversation with Dr. Harold Hodge).

3. Rapaport claimed to show an association between fluoridated water supplies and Down's Syndrome.

A series of studies by Rapaport were reported in 1956, 1959, and 1963. The author's 1956 publication was very incomplete. Children with Down's Syndrome (DS) in Wisconsin, Illinois, and North and South Dakota were ascertained. Illinois and Wisconsin were analyzed separately. North and South Dakota data were pooled and analyzed together. DS children admitted to special institutions were recorded and in Illinois, this did not occur until the children were at least 5 years old. Rapaport claimed that there was an association between fluoridated water supplies and the prevalence of Down Syndrome.

The 1959 report focussed only on ascertaining DS in Illinois over a 6 year period. Data came from birth and death certificates as well as special institutions. Once again, the authors claimed a statistically significant increase in DS cases in high fluoride areas compared to low fluoride areas.

The 1963 publication simply reported the first two studies.

A number of problems with the studies leave little confidence in the results.

(1) The author did not provide age-standardized rates. This is important since maternal age is known to be associated with DS. There was a comparison of the woman's age of 240 (out of 687) DS cases in the first study. Mean maternal age in high-fluoride areas was less than mean maternal age in low-fluoride areas.

In the second study, the only age comparison was whether women were 40 or older.

Role of Female Age

F(mg/1)	Total # Cases	Mother's Age (40 & over)	
		# of cases	%
0.0-0.2	67	16	23.0
0.3-2.6	81	9	11.1

Neither of these methods are adequate means of controlling for this important confounder.

(2) There is a significant underascertainment of cases, due to the fact that only institutional records are relied upon. The second study used birth and death certificates but not all cases were ascertained. Underascertainment of cases may not itself represent a bias, if ascertainment was equal between high and low fluoride towns. The authors made no attempt to determine this. Thus, the effect of the underascertainment is unknown. It is interesting to note that the DS rate in low-fluoride towns (0.0-0.7 ppm) was 1 in 2663, while for high-fluoride towns, the rate was 1 in 1400. The normal DS rate, given full ascertainment, is about 1 in 600-700 births. Both of Rapaport's rates are considerably less than expected. It is also evident that the rate of DS ascertained in high fluoride towns was about twice that of low fluoride towns. This could very well reflect a difference in the degree of ascertainment rather than a true difference in DS rates.

(3) In the first study, the DS births were compared with the total population in the area, and not with births in the area. Computing rates using total population rather than births may not give an accurate indication of DS, since there may be a difference in the number of births betweeen different populations.

(4) In the first study, the hospital of birth rather than the place of birth was correlated with fluoride status of the town. Since many women from rural areas (with different fluoride status) may come to the city to give birth, it is important to correlate fluoride status with the place of residence of the woman during pregnancy. This would assure that the DS cases in the numerator are a part of the population in the denominator.

All of the above could greatly affect the outcome of the studies. Thus, the "positive results" from Rapaport come from seriously flawed analyses. Furthermore, no study has been able to confirm Rapaport's findings, despite many attempts to do so. A discussion of studies showing no association follows.

4. There are a number of well done epidemiological studies that show no association between water fluoridation and DS.

Some of the studies that have failed to show an association between DS and fluoridated water supplies have been well done.

Needleman et al (1974) ascertained nearly all DS cases in Massachusetts between 1950-1966. Data were gathered from hospitals, the Department of Public Health, the Department of Mental Health, nurseries and schools for mentally retarded, karyotyping labs, birth and death certificates, and other sources. During this period, 30 communities introduced fluoride into their water systems. The analysis was limited to these 30 towns to control for unknown confounding factors. Mean maternal age was 34.2 for non-fluoride cases, and 34.0 for fluoride cases. No significant difference was observed between the number of DS cases born to fluoride mothers and those born to non-fluoride mothers.

Prevalence Rates of DS at Birth among Live Offspring of Mothers Living in Fluoridated and Non-fluoridated Communities

	F Group	Non-F Group
Cases	124	148
Births	81,017	101,753
Cases/1000 births	1.53	1.46

This study had good statistical power. The authors could conclude, with 95% confidence, that a 20% or greater increase in risk attributable to fluoridation for DS could be excluded.

A study by Erickson et al (1976) also concluded no association could be shown between DS and fluoride status of the town. The study was based on reviewing over a million live births in Metropolitan Atlanta (from the Metropolitan Atlanta Congenital Malformations Surveillance Program, 1960-1973, which ascertained cases via regular staff visits to all hospitals with obstetric or pediatric services in the Atlanta area) and other areas around the country (from the National Cleft Lip Palate Intelligence Service, 1961-1966, ascertained via birth certificates). Rates for 10 different congenital malformation categories, including DS, were computed. The authors addressed the problem of underascertainment. They ranked the malformation rates from highest to lowest, and then looked at the fluoride status of the areas with those rates. The fluoride status was randomly distributed throughout the ordering of rates. Therefore, little bias existed in the reporting of DS between high and low fluoride areas.

DS rates were standardized for age, and noted the place of residence at birth. No association was found. The only statistically significant difference was in the age category of 35-39, where DS was higher in the non-fluoride areas.

Table 2 ■ Maternal age specific incidence of Down's syndrome in areas with and without fluoridated water.

	Metropolitan Atlanta, 1960-1973				
	Fluoride (166,186 total births)		Nonfluoride (101,639 total births)		X^{2*}
Maternal age (yr)	No. cases	Rate/10,000 white births	No. cases	Rate/10,000 white births	
<19	19	7.7	7	3.8	1.98
20-24	41	6.9	15	4.0	2.93
25-29	34	6.8	11	4.1	1.78
30-34	25	11.3	13	11.0	0.01
35-39	15	18.5	25	45.8	7.42
≥40	32	165.3	13	85.1	3.67
Total	166	10.0	86†	8.5	1.41

*1 degree of freedom corrected for continuity, $P\ 0.05 = 3.84$.
†Includes two cases of unknown maternal age.

NIS surveillance areas, 1961-1966				
Fluoride (234,300 total births)		Nonfluoride (1,032,100 total births)		X^{2*}
No. cases	Rate/10,000 white births	No. cases	Rate/10,000 white births	
8	3.2	30	2.3	0.39
19	2.2	75	2.0	0.04
22	3.6	76	2.8	0.74
18	5.1	76	4.8	0.01
20	10.0	126	16.4	3.90
28	48.3	141	57.3	0.53
115	4.9	524	5.1	0.08

A later study by Erickson (1980) looked at over 636,000 white births, from which 268 cases of DS were ascertained. The data came from birth certificates (1973-1975) from the U.S. National Center of Health Statistics. The author compared rates between cities (≥250, 000) with ≥ 5 years of fluoride with cities that had not been fluoridated. This time, no difference was found in any age-adjusted category. The overall age-adjusted rates were 4.1 and 4.4/10,000 live births in the fluoride and non-fluoride categories, respectively.

TABLE 2. Rates of Down syndrome by maternal age and fluoridation category†*

Maternal age	Fluoridation category		
	Fluoridated	Non-fluoridated	Total
≤ 19	1.8 (12)	2.9 (10)	2.2 (22)
20-24	1.9 (29)	2.8 (20)	2.2 (49)
25-29	3.7 (50)	2.9 (18)	3.4 (68)
30-34	5.3 (30)	4.8 (12)	5.2 (42)
35-39	16.1 (30)	17.6 (14)	16.6 (44)
≥ 40	60.5 (28)	82.2 (16)	67.0 (44)
Total	4.1 (178)	4.4 (90)	4.2 (268)

*Rates per 10,000 live births; number of cases of Down syndrome in parentheses.
†Whites only.

Knox et al (1980) compiled DS cases in Birmingham, England from 1950-1974 (with follow-up to 1978). Ascertainment was good, relying on birth and death certificates, and hospital and health visitor records. The authors allowed a 4 year period of follow-up to improve detection of DS cases.

Between 13,800 and 22,000 total births were recorded per year. In 1964, Birmingham fluoridated its water supply. The authors compared before and after DS rates, standardizing for maternal age.

Standardized Prevalence of Down's Disease (#/thousand births)

BEFORE			AFTER	
1950-54	1955-59	1960-64	1965-69	1970-74
1.46	1.68	1.54	1.60	1.58

No significant differences were noted, and the authors concluded fluoride exerted no effect on the prevalence of DS. Further, the authors reviewed data for many other malformations and found no relationship between these specific malformations and fluoridation of water.

Another study was done in 1958 by Berry. The author found no association between fluoride and DS. The study did not standardize for age, and involved smaller numbers. It is therefore not as good as the later studies.

The possibility that a long induction period until effects may be observed has not been ruled out. It is of interest, therefore, to investigate the pregnancy outcomes of women who had themselves been exposed in utero.

In conclusion, the original Rapaport studies were seriously flawed. They remain the only human studies that have shown an association between fluoride and DS. Since then, five studies have shown no association, four of which were well done, and which have good statistical power. Therefore, on the basis of these studies, there is no convincing evidence that fluoridated water supplies are associated with a higher incidence of DS.

5. Data from Collaborative Perinatal Project

A prospective study of over 50,000 pregnancies was undertaken in what became known as the Collaborative Perinatal Project. In a book published out of this study, Birth Defects and Drugs in Pregnancy, data were presented on drugs used by pregnant women in relation to birth defects in children.

Fluoride was one drug that was investigated. The data are quite sparse, since there were only 122 exposures (i.e, when considering drug use during the first four lunar months of pregnancy). The exposures noted in the study were by supplemental intake of fluorides, and not by water fluoridation. No data were given on the dosages of fluoride. The following two tables show the results:

Table 32.1

Children (3,248) With Any Malformation in Relation to Exposure to **Inorganic Compounds and Certain Vitamins** During Lunar Months 1–4 Among 50,282 Mother-Child Pairs

	No. of Mother-Child Pairs Exposed	No. of Malformed Children	Crude Relative Risk	Hospital Standardized Relative Risk[1]	Survival and Race Standardized Relative Risk[1]
Inorganic compounds and certain vitamins	2,542	184	1.13	1.07	1.10
Bromides, fluorides, and iodides	1,526	121	1.24[2]	1.17	1.20
Fluorides	122	11	1.40	1.39	1.39
Iodides	489	38	1.21	1.11	1.10
Bromides	986	77	1.21	1.16	1.22
Calcium (parenteral), iron, and vitamins	1,091	65	0.92	0.87	0.91
Calcium compounds (salts)	1,007	61	0.94	0.88	0.93
Iron, i.m.	66	3	0.70	0.68	0.66
Vitamins B_{12} and K[3]	28	1	0.55	0.50	0.45

[1]Estimated by the Mantel-Haenszel procedure
[2]$X^2_1 = 5.38$, $p < 0.05$
[3]Phytonadione (14); cyanocobalamin (11); liver extract, i.m. (6)

Table **32.2**

Children (2,277) With Malformations Showing Uniform Rates by Hospital in Relation to Exposure to **Inorganic Compounds and Certain Vitamins** During Lunar Months 1–4 Among 50,282 Mother-Child Pairs

	No. of Mother-Child Pairs Exposed	No. of Malformed Children	Crude Relative Risk	Hospital Standardized Relative Risk	Survival and Race Standardized Relative Risk
Inorganic compounds and some vitamins	2,542	130	1.14	1.10	1.11
Bromides, fluorides, and iodides	1,526	86	1.25[1]	1.21	1.19
Fluorides	122	9	1.63	1.65	1.62
Iodides	489	27	1.22	1.16	1.04
Bromides	986	54	1.21	1.18	1.22
Calcium (parenteral), iron, and vitamins	1,091	45	0.91	0.88	0.93
Iron, i.m.	66	2	0.67	0.66	0.63
Vitamins B_{12} and K	28	1	0.79	0.75	0.70
Calcium compounds	1,007	42	0.92	0.89	0.95

[1] $X^2 = 4.20 < 0.05$

The authors concluded that "Fluorides (122 exposures) gave minimal, if any, evidence of association with malformations, but numbers were small" (Heinonen et al, pg. 408).

When considering fluoride intake at any time during the pregnancy, the standardized relative risk for fluorides was 0.816 (1422) exposures), with a 95% C.I. of 0.55-1.32.

6. Animal Studies

Well controlled animal studies with diets containing 70-880 mg/kg fluoride demonstrated a decrease in litter production in rats and pigs, and delayed estrous, repeated failures to conceive, decreased birth weight and lowered viability in cattle. With lower fluoride dosages (60 mg/kg and less), reproductive performance in animals has almost without exception been satisfactory (Smith et al, 1982). For example, a series of studies were done where cattle were given 12, 27, 49 and 93 mg/kg fluoride in the diet (Shupe et al, 1963). The authors concluded that prolonged ingestion of fluoride had no effect on reproduction.

At high dosages, fluoride has been embryo-and fetotoxic in animals. A dose of 30 mg/ 1 water of NaF at 6-15 days of pregnancy in rats produced a significantly greater number of congenital malformations in the offspring (Larez et al, 1980). Only one experimental group was compared with controls. Maternal weight change was not significantly different between the groups and there appeared to be no overt maternal symptoms. No difference was seen in the number of live fetuses between the groups. No histological differences were seen. The only difference was in the number of resorptions (5.34% in controls and 10.27% in treated), runt fetuses (2/177 in controls and 11/183 in treated), and bone changes in the sternum and parietals.

Larez et al estimated that 1.1 mg of fluoride was consumed by the rats per day. This would correspond to a total dose in a 50 kg woman of 170 mg of fluoride per day.

Water is fluoridated to concentrations of 1 mg fluoride/liter water. Assuming a woman drinks 1 liter (about 1 quart) of water per day, her total dose from fluoridated water would be 1 mg fluoride per day.

Devoto et al (1972) gave rats 1, 5, 10, 15 and 20 mg/kg fluoride daily (intraperitoneal and subcutaneous injection) on days 10-18 of pregnancy. The authors found a greater percentage of dead fetuses at all levels in the intraperitoneal groups. In the subcutaneous groups, the percentages of dead fetuses went from 2% in the control to 4% in each of the 1 and 5 mg/kg groups, to 25% in the 10 mg/kg group. A 1 mg/kg dose corresponds to a 50 mg dose in a woman. A 10 mg/kg dose corresponds to a 500 mg dose in a woman.

Dose	% Dead Fetuses					
	0	1	5	10	15	20
intraperitoneal	2	14	10	18	17	25
subcutaneous	2	4	4	25	15	16

The authors suggested that the toxic action of fluoride was in the placenta, and that the death of the fetus was secondary to a lack of adequate placental nutrition. No pathological changes were noted in the placenta of healthy fetuses. The authors cautioned that in considering whether these results apply to man, man does have a different type of placenta than the rat. The structure of the placenta is different in rats compared to humans. The differences may allow easier movement of chemicals across the placental barrier. The intraperitoneal and subcutaneous routes also result in much more rapid absorption, and much higher peak concentrations than the normal route of ingestion or inhalation.

Fluoride given to pregnant animals may interefere with growth and development of skeletal tissues. Glock (1940) claimed that fluoride retarded calcification in the fetuses of rats given 50 ppm in the drinking water. The study only used one dose level to compare with controls. The animals were given 15 cc/day and the author did not state how many animals were used.

In an abstract, Paynter and Grainger (1956) reported on a study of about 300 rats. The authors concluded "When measurements of teeth of animals raised on a diet containing 10-22 ppm fluoride were weight adjusted, it was found that these teeth were smaller than those in control animals of their size." No details were given on the conduct of the study. Thus, it cannot be critically evaluated.

Fleming and Greenfield (1954) concluded that fluorides interfered with the growth and development of teeth and skeletal tissues in the offspring of mice given NaF or CaF_2 during gestation. Some mice were injected with NaF or CaF_2 while others were given water containing NaF or CaF_2. Total dosages via drinking water were not precisely known, since it depended on the intake of water. The dose was administered at different times during pregnancy to different animals. The total amount via injection was 100 ug/day. For drinking water, the minimal total amount was estimated at 60 ug/day. While 245 pregnant mice were exposed to fluorides, and 25 mice served as controls, the authors did not report overall outcomes of the experiment. They did report on teeth changes of 5 neonatal mice who ha been exposed in utero.

SUMMARY OF ANIMAL DATA

	Dose at which effect observed	Effect	Conversion to Human Female Total intake/day*
rats (Larez et al, 1980)	- 30 mg F/1 water (37 ml water/day) - 1.1 mg F/day consumed	-↑resorptions -↑runt fetuses - bone changes	- mean maternal rat weight 325 g - human dose 170 mg/day
rats (Devoto et al, 1972)	- 1 mg/kg(intraperitoneal injection)	-↑in number of dead fetuses	- 50 mg/day (no body weight of rats given)
rats (Glock, 1940)	- 50 mg F/1 water (15 cc of water/day) - 750 ug F/day consumed	- retarded calcification in fetuses	- 110 mg/day (no body weight of rats given)
rats (Paynter & Grainger, 1956)	- 10-12 mg/kg diet	- smaller teeth	- 500-600 mg/day (no body weight of rats given)
mice(Fleming & Greenfield, 1954)	- 60-100 ug/day	- retarded calcification of teeth of offspring	- 100 mg/day (no body weight of mice given)

*ASSUME

-rat weight of 350g (where not given)
-mouse weight of 30g (where not given)
-human female weight of 50 kg

Dose from water fluoridated at optimal level of 1 mg fluoride/ liter water, assuming 1 liter water consumed per day, is equal to 1 mg per day of fluoride.

"Retardation of the calcification of bone and of tooth structure was consistently observed, with the regular appearance of cartilaginous substances in the areas adjacent to the teeth and also within the pulp chambers. In addition, there were structural changes in the ameloblasts and the appearance of cartilage-like cells in the pulp in place where odontoblasts are normally found" (Feming and Greenfield, 1954, pg. 785).

7. Interpretation of Animal Studies

The species that showed effects at the lower levels were rats and mice. The most serious limitation in extrapolation to humans is the difference in structure and possibly different function of the placenta as compared to humans. This was pointed out in the study by Devoto et al, where the authors cautioned an extrapolating their result to humans, especially since the effects observed were due to necrotic placenta.

Teratogenic effects vary in different species and in different strains of the same species. For example, thalidomide, the most potent human teratogen known, produces little, if any, effect in the rat and mouse. The smallest dose in man producing an effect is 0.5-1.0 mg/kg. In mice and rats, the largest dose that produced no effect was 4000 mg/kg. On the other hand, aspirin is safe in humans but produces a high incidence of malformations in rats. Cortisone produce 100% cleft palate in certain strains of mice, but no known effect on other strains.

The difficulty of extrapolating results in animals in teratology testing to humans has been noted by workers in the field. Dr. David Blake of Johns Hopkins discussed results of the Collaborative Perinatal Project and compared these findings with results in animal testing. He wrote "...the obvious conclusion is that in vivo teratologic tests have poor predictability of human teratogenic potential. Generally stated, it would appear that most drugs can be found to be teratogenic in some animal models, while very few drugs have a clinically significant teratogenic potential" (Blake, 1980, pg. 222).

There is also the question of what dose level to test in order to see an effect. It is well known that high doses must be given in carcinogenicity tests in order to see an effect in small groups of animals. Wilson commented:

> The unfounded assumption that carcinogenicity and mutagenicity bear more or less close similarity to teratogenicity has resulted in erroneous assumptions about dose-response relationships in the latter. Mutations and cancers often appeared to have a straight-line dose-response relation, i.e., incidence is proportional to dosage at all levels above zero, although this also has been debated. Nevertheless, if there are no-effect levels for carcinogenesis and mutagenesis, they are sufficiently low to make the matter arguable, which seems not to be the case for teratogenesis (Wilson and Fraser, 1977).

Wilson also pointed out that the dose-response curve for most embryotoxic effects have a steep slope, sometimes going from minimal to maximal effect levels by simply doubling the dose. This again points out that teratogens do not necessarily lack a threshold. An effect at a high dose does not necessarily mean that there will be an effect at a lower dose.

From a recent article extensively reviewing data on fluorides and pregnancy, it was noted: "Dietary fluorides (0.5-1.5 mg/day) plus fluorides from fluoridated drinking water (0.7-1.1 ppm) have no known ill effects. One of us...has, for three decades, searched diligently for substantive evidence of injury to sick or well, old or young: none has been found" (Smith et al, 1982, page 33). In the animal data, most effects noted at the lower levels (which were still high) were not major, i.e., histological changes in teeth, and retarded calcification. This contrasts with known beneficial effects on dental health when water is fluoridated at the optimum level of 1 ppm.

8. Another area of concern is genetic damage that may be caused by fluoride.

Concern over the possibility that fluoride may cause genetic damage arose after Mohammed and Chandler reported that chromosomal abnormalities of mice given 1 mg fluoride/l dose were more numerous than those of the controls. This study has never been published although the data were presented in Congressional hearings. The results were also presented before a meeting of the American Chemical Society, and appeared as an abstract in a journal. In the experiment, male BALB/c mice were given distilled water with different levels of fluoride (0, 1, 5, 10, 50, 100, 200 mg/l). At 3 and 6 weeks, 4 mice of each group were sacrificed and examined for chromosomal damage. The authors said that the number of cells with chromosomal abnormalities increased with fluoride dose of 1 mg/l or greater.

The results have come under strong criticism from a number of sources. The mice used were highly inbred (over 120 generations) and had a low incidence of spontaneous malformed young and low rate of spontaneous tumor development. Furthermore, the mice had been raised for generations on fluoride water and showed no signs of genetic instability. One reviewer noted:

> The draft of the paper available for review by the National Academy of Science in 1977 contained errors and omissions which were disturbing. The bone values were less than any previously published for low fluoride diets even though some of Mohammed and Chandler's mice received 200 NaF in their water for six weeks! Also, the original Table V showed many percentages which could not be derived from any whole number of abnormalities given the number of cells they said they examined. The published paper (Mohammed and Chandler, 1977) contains over 70 changes in the Table V. How the decisions were made regarding the number of slides prepared per group and how many cells were counted on each slide or whether this was done blindly, was not indicated (Johansen et al, 1978, pg. 303).

9. Other in vivo studies have been negative.

A well conducted experiment by Martin et al (1979) involved 2 strains of mice, including the strain used by Mohammed and Chandler. In Swiss Webster mice, the animals were given either 0 or 50 mg/l fluoridated water for their entire lifetime. They were sacrificed and the chromosomes examined. In BALB/c mice the animals were given either 0, 1, 5, 50 or 100 mg/l fluoride for 6 weeks. They were sacrificed and the chromosomes examined. In both experiments, the exams were blind.

10. In vitro results.

Jagiello and Lin (1974) experimented with mammalian oocytes (mouse, sheep, cow). Exposures were 400, 200, 100 and 10 ppm NaF. Cytological changes were seen in the cow and ewe oocytes. There were little or no effects of fluoride on chromosomes in mouse oocytes up to 200 ppm fluoride up to 14 hours. Sheep and cow oocytes showed cytological changes at 100 ppm fluoride.

Similar results were reported by 2 other authors (Cass, 1961, Hodge and Smith, 1965).

There have been no tests with Salmonella typhymurim nor with Drosophila melangogaster showing the mutagencity of NaF. There have been no positive dominant lethal or recessive lethal tests except for Mohammed and Chandler, a study criticized by the International Agency for Research on Cancer (IARC) for its unusually low spontaneous mutation rate. There have been no positive SCE tests, nor any positive tests with human lymphocytes.

Cytogenetic abnormalities have been observed in plants after various types of exposure.

There is some suggestion that fluoride may reduce DNA repair synthesis following high doses of radiation in mouse spleen cells, thereby affecting the response after exposure to known mutagenic agents (Klein et al, 1974). The significance of this is not known.

In sum, several experts have concluded no evidence exists that fluoride is mutagenic for any mammal.

1. The IARC (1982) noted "Sodium fluoride was not mutagenic to Salmonella typhimurium or Drosophila melanogaster and did not induce gene conversion in Saccharomyces cerevisiae".

2. "While...studies suggest that fluoride and HF in high doses may be weak mutagens in Drosophila, they are far from having demonstrated that fluoride has a mutagenic potential in humans" (Johansen et al, 1979, pg. 308).

3. Dr. Harold Hodge, in a review of over 40 mutagenicity studies (to be published), concluded that fluoride is not mutagenic.

11. It is concluded that fluoride poses no known risk to the fetus and the mother at the levels that are seen when water supplies are fluoridated at the optimal level of 1 ppm.

Fluoridated water poses no known risk to the pregnant woman and fetus.

(1) There is no convincing evidence that fluoridated water is associated with DS.

(2) Data from animal studies show effects only at very high dosages.

(3) There is no convincing evidence that fluorides have mutagenic potential in humans.

On the other hand, the benefits of fluoridation in reducing dental caries in children are widely acknowledged. This is based on the following:

(1) Fluoride naturally in community drinking water supplies is associated with reduced numbers of decayed, missing, and filled permanent teeth of 12 to 14 year old residents never absent from their homes for more than 30 days. With increasing fluoride concentrations from traces (e.g., 0.1 ppm) to about 1 ppm, caries experience decreases on the average from seven to ten decayed, missing, and filled teeth per child to two to three per child.

(2) Lower caries rates extend into the adult life of residents who remain in naturally fluoridated communities and continue to drink water.

(3) Fluoride in optimal concentrations added to drinking water supplies naturally low in fluoride confers on children drinking such fluoridated water the degree of tooth health found in children drinking water containing optimal concentrations naturally (Smith et al, 1982, pg. 33).

MS/ch